## REMARKS

The spelling of "hemodialysis" in the claims has been amended into conventional American spelling.

Claim 1 has been amended to make it clear that the patients being treated are patients suffering from oxidative stress as a result of hemodialysis treatment, which treatment is itself the result of chronic kidney disease. To expedite prosecution, claims to compositions and other methods of treatment have been canceled. Support for revised claim 1 is found at page 3 lines 12 and 13 of the specification.

It is believed that as amended the claims meet all of the pbjections raised and clompy with the clarity requirements of 35 USC 112 paragraph 2.

So far as the written description rejection is concerned, the claims are now clearly directed to treating or preventing oxidative stress in hemodialysis patients. As noted above, this concept is clearly described at page 3 lines 12 and 13 It is therefore clear that the applicants were in possession of this concept at the time of filing the application. The examiner's reference to a plethora of possible conditions and pathologies of distinct etiologies is not understood. As stated in the opening paragraph of the application, the invention relates to treatment of oxidative stress resulting from hemodialysis treatment. Page 1 lines 14 to 22 set out the cause as follows:

> Oxidative stress has been observed to be particularly evident in patients suffering from kidney failure and undergoing haemodialysis. This phenomenon is attributed to bioincompatibility between the patient's circulating blood cells and the dialysis membranes, together with other factors such as a chronic uraemic state. This bioincompatibility leads to excessive production of Reactive Oxygen Species (ROS) by the immune system, and at the same time a reduction in the antioxidant capacity of the

> body due to losses of antioxidant molecules such as glutathione (GSH), vitamin A, vitamin C and vitamin E through the filters of the dialysis membranes.

The basis for the invention is therefore clearly set out. There is no need to speculate further on other etiologies as the examiner implies.

The examiner further states that there is lack of a written description because "the skilled artisan could not 'immediately envisage' the claimed methods based on the description provided in the disclosure." This is not understood. What more is needed than a statement as to the compounds to use (given at page 3 lines 11 - 12), the amounts to use (original claim 3) and the method of administration to be used (page 3 line 16) for one skilled in the art to be able to "envisage" the invention. The examiner implies that specific therapeutic endpoints should be given. The basis for this is not stated nor is applicant's attorney aware of any rule or case law that requires this. As applicant's attorney understands the law, the written description requirement is met by describing the invention in such a way that one skilled in the art can understand what the invention is. There is a separate enablement requirement that requires that the description should be sufficient to enable one skilled in the art to put the invention into practice without undue experimentation and finally there is a requirement that the invention must be useful and that if the examiner believes that the invention as stated is not credible he or she can put forward plausible reasons for this belief and if this is done then the burden of showing that the invention works passes to the applicant (PTO utility Guidelines). None of these, however, sets out any requirement to set out a therapeutic end point.

In the corresponding application before the European Patent Office the question of efficacy was raised and the applicants responded by submission of a test note. A copy of that note is submitted herewith. Although not directly related to any of the specific issues raised by the Examiner, this test note does address what it seems may be part of the examiner's concern. As can be seen from the test note, the invention is indeed effective.

It is submitted that the specification meets the written description requirement of 35 USC 112 paragraph 1.

So far as the question of enablement is concerned, as noted above, the claims have now been limited to administration of cystine, cysteine or mixtures thereof to those, suffering from oxidative stress due to hemodialysis. One skilled in the art should have no difficulty in doing this based on the present description.

The examiner sets out the Wands factors.

The applicants agree that there can be differences in how chemical act in the body under different circumstances. However, in the present case, we are not concerned with interactions with complex proteins that may take different forms depending on a patients genetics but rather with reactions with reactive oxygen species resulting from interaction of patients blood cells and dialysis membranes. Claims to treatment of chronic renal failure as such have been canceled and so the examiner's comments on this are now moot.

It is true that there are no working examples in the specification. But the case law does not require them. **Falkner v. Inglis** 79 USPQ2d 1001 (Fed. Cir. 2006). So far as the question of "prevention" is concerned, the applicants again recognize that there may be times when something more is needed to justify a claim for this than is required for a claim to treatment. It is, however, submitted that in the present case, prevention is in fact merely "100% treatment" and reference to this in the claim is appropriate to avoid infringement when the treatment is so effective that oxidative stress is avoided. This is simply a distinction of degree rather than of substance and in the present circumstances the reference to prevention should be permitted to remain.

On the question of the quantity of experimentation, the examiner's comments seem

directed to treatment of acute or chronic kidney failure. Since the claims are no longer directed to treatment of these conditions, they appear to be moot.

In view of the fact that one skilled in the art can carry out the invention claimed without undue experimentation, it is submitted that the enablement requirement of 35 USC 112 has been met.

We turn now to the rejection under 35 USC 103 based on the combination of U.S. 4,794,124 (Yamamoto) with The Merck Manual and WO 00/53176 (Dall'Aglio).

Yamamoto describes the use of cysteine to treat diabetic complications. Asstated at column 1 lines 57 - 65,

> The present inventors early focused attention on cysteine which is a constituent amino acid of glutathione which is known to be essential to the maintenance of crystalline lens transparency and conducted a series of studies on the pharmacologic effects of this amino acid. The studies led to the finding that cysteine has a very remarkable therapeutic effect on diabetic complications and particularly on diabetic cataract. The present invention is predicated on the above finding.

It is true that the specification talks generally about use of cysteine to treat diabetic complications, but the only definite information given is with respect to cataracts and that in rats treated with cysteine, serum chemical parameters were close to normal in male SD rats in which diabetes had been induced by streptozotocin injection. Although Yamamoto does not say so, it is understood that streptozotocin induces diabetes by destruction of pancreatic cells thereby preventing insulin production. This is therefore an insulin-dependent form of diabetes (Type 1). The types of condition referred to in the present claims are typically those resulting from non-insulin dependent diabetes.(Type 2) It is not clear that teaching that a treatment will restore chemical parameter levels in insulin dependent rats will be a predictor as to what will happen to chemical levels in other types of diabetes. Insulin dependent diabetes is normally treated by

insulin injections rather than by hemodialysis.

Merck simply indicates that "diabetes" is the most common cause of end stage renal disease. It is also stated that "If uremia results fro a progressive and untreatable disorder, conservative management is palliative until dialysis or transplantation is required.

Dall'Aglio teaches that cysteine may be used to treat conditions caused by oxidative stresses and alterations of mitochondrial energetic metabolism. Diabetes (of no particular type) is mentioned as one of a large number of possible causes of oxidative stress.

The art therefore teaches that cysteine can be used to treat diabetes. It also teaches that kidney disease may be caused by diabetes. It does not, however teach or in anyway suggest that specific problems that arise when patients are subject to hemodialysysis may be treated or prevented by use of cysteine. The present claims are limited to this and are therefore novel and non-obvious over this art. In particular claim 10 is specifically directed to a method in which the relationship of the treatment with cysteine or cystine with the dialysis is specifically set out.

It is therefore submitted that the requirements of 35 USC 103 have been complied with and that this application should be allowed.

Respectfully submitted,

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